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DOI: <https://doi.org/10.2165/11632440-000000000-00000>

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ZORA URL: <https://doi.org/10.5167/uzh-69166>

Journal Article

Accepted Version

Originally published at:

Jacobs, Robert A; Lundby, Carsten; Robach, Paul; Gassmann, Max (2012). Red blood cell volume and the capacity for exercise at moderate to high altitude. *Sports Medicine*, 42(8):643-663.

DOI: <https://doi.org/10.2165/11632440-000000000-00000>

Red blood cell volume and the capacity for exercise at moderate to high altitude

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Short Title: Red blood cell augmentation and exercise in hypoxia

Word Count: 6,804

Tables included: 5

Figures included: 2

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Abstract (217)

Hypoxia-stimulated erythropoiesis, such as that observed when red blood cell volume (RCV) increases in response to high altitude exposure, is well understood while the physiologic importance is not. Maximal exercise tests are often performed in hypoxic conditions following some form of RCV manipulation in attempt to elucidate oxygen transport limitations at moderate to high altitudes. Such attempts, however, have not made clear the extent to which RCV is of benefit to exercise at such elevations. Changes in RCV at sea level clearly have direct influence on maximal exercise capacity. At elevations above 3,000 m, however, the evidence is not that clear. Certain studies demonstrate either a direct benefit or decrement to exercise capacity in response to an increase or decrease, respectively, in RCV; whereas, other studies report negligible effects of RCV manipulation on exercise capacity. Adding to the uncertainty regarding the importance of RCV at high altitude is the observation that Andean and Tibetan high-altitude natives exhibit similar exercise capacities at high altitude (3,900 m) even though Andean natives often present with a higher percent hematocrit (Htc) when compared to both lowland natives and Tibetans. The current review summarizes past literature that has examined the effect of RCV changes on maximal exercise capacity at moderate to high altitudes, and discusses the explanation elucidating these seemingly paradoxical observations.

Keywords: hematocrit, VO₂max, hypoxia, oxygen flux, optimal hematocrit, critical PO₂

Abbreviations: red blood cell volume (RCV); hemoglobin (Hb); percent hematocrit (Htc); fraction of inspired oxygen (FiO₂); partial pressure of oxygen (PO₂); partial pressure of alveolar oxygen (PAO₂); partial pressure of arterial oxygen (PaO₂); arterial oxygen saturation (SaO₂);

arteriovenous oxygen difference (a-v O₂); alveolar to arterial PO₂ difference (A-aDO₂); mixed
venous partial pressure of oxygen (PvO₂); arterial oxygen content (CaO₂); diffusive capacity of
oxygen of skeletal muscle (DmO₂); exercise-induced arterial hypoxemia (EIAH); minute
ventilation (V_E); oxygen consumption (VO₂); maximal oxygen consumption (VO_{2max}); time to
exhaustion (TTE); erythropoiesis stimulating agent (ESA); erythropoietin (EPO); erythropoiesis-
stimulating agent (ESA); novel erythropoiesis stimulating protein (NESP); recombinant human
erythropoietin (rhEpo); central nervous system (CNS); not significant (NS); whole body (WB);
not applicable (N/A); leg blood flow (LBF), two leg blood flow (2LBF); systemic vascular
conductance (SVC), leg vascular conductance (LVC); mean arterial pressure (MAP); heart rate
(HR); cardiac output (Q); kilopond per meter (kpm); respiratory exchange ratio (RER); treatment
(Tx); lactate concentration ([La]); Watts (W); hypoxia-inducible factor 2 alpha (HIF-2α); sea
level (SL); intermittent hypoxia (IH)

Introduction

The study of both acclimatization and adaptation to hypoxia in humans is a timely topic of current research. Approximately 16.5 million km² of the earth's surface exists at or above an elevation of 2,000 m¹. More importantly, between 140 and 150 million people reside at these high altitudes, while another 35 million lowland dwellers visit or commute to elevation above 3,000 m annually^{2,3}. Exposure of humans to such altitudes is a challenge to homeostatic maintenance of oxygen flux as a result of the gradual decrease in the partial pressure of oxygen (PO₂) attendant to the diminishing barometric pressure⁴. Our understanding regarding the physiologic importance of red blood cell volume (RCV) at high altitudes is important, as the erythrocyte is the primary means of transporting oxygen from the environment to respiring cells. In this review, RCV is referring to the total number of erythrocytes in the blood as oppose to volume of individual red blood cells. Research examining this area of interest has presented seemingly conflicting results.

The overall aims of this review are as follows: i) To review maximal exercise capacity near sea level (0 to 500 m), and the effect of increasing RCV in these conditions; ii) To introduce the topic of study regarding the function of RCV and exercise capacity at elevations ranging in between 2,000 to 5,500 m; iii) To summarize the literature that has studied the role of RCV manipulation on the ability to exercise at elevations ranging from moderate to high altitude; and iv) To discuss these seemingly paradoxical observations.

The initial set of studies included in the review were retrieved through a search of PubMed and Web of Science using the keywords acclimatization, exercise, high altitude, percent hematocrit

(Htc), and red blood cell. Only those studies that had corresponding measurements of exercise performance with Htc, total hemoglobin (Hb) mass, or total arterial oxygen content (CaO_2) at baseline, and following an intervention (e.g., acclimatization to a given altitude, hemodilution, blood infusion, or erythropoietin (EPO) administration) fulfilled our criteria, and were selected. Preferable studies were those that had measurements for either Htc, or total Hb mass in conjunction with CaO_2 . From those primary studies, we established both forward and backward reference mapping for potential studies of interest that were initially missed through the database searches. Again, studies of interest were examined, and only those that met the previous selection criteria were included in this review. Overall, 20 studies fit our criteria and have been included in this review (Tables 1-4).

This topic has been presented in several independent studies, but to the best of our knowledge never collectively in a publication that assembles and interprets all relevant literature together. In this way, the present review shall contribute to our understanding of the actual impact of RCV and attendant CaO_2 on exercise capacity at altitude. In our effort, we attempt to cover the whole spectrum of RCV manipulations including acclimatization, acute reductions (hemodilution), acute expansions (transfusion), and finally more chronic expansion of RCV (via an erythropoiesis-stimulating agent, ESA), and how these manipulations affect exercise at moderate to high altitude. The limitation of this review is the lack of data dealing with exercise capacity in polycythemic highlanders prior to, and following hemodilution. This may be of interest for future research.

The relationship between oxygen transport and exercise capacity from sea level to higher elevations

Exercise capacity at sea level tightly correlates with RCV⁵. The fact that an individual's aptitude for exercise, both maximally⁶⁻¹² and/or submaximally^{6, 7, 9, 11, 13}, improves near sea level following increases in RCV is well understood¹⁴. This improvement in exercise performance is mostly a direct result of the increase in CaO_2 that is concomitant to increases in RCV^{8-10, 15-17}. Alternative means of adjusting CaO_2 , such as hyperoxic breathing, increases exercise performance not only at sea level, but also at higher elevations^{18, 19}; though the added bulk of equipment necessary for oxygen supplementation is not conducive for most exercising athletes. Interestingly there is evidence suggesting that hyperoxic breathing may be more advantageous when attempting to improve maximal oxygen consumption ($\text{VO}_{2\text{max}}$) than methods used to increase RCV, such as blood transfusions, or treatment with an ESA. The ratio of $\Delta\text{VO}_{2\text{max}}$ per ΔCaO_2 appears greater with hyperoxic breathing (2.06)^{18, 19} when compared to increases in RCV (0.70)^{8-11, 17} at sea level. Maximal workload has also been shown to significantly increase (233 ± 15 W to 283 ± 18 W) after acclimatization to 5,260 m when increasing hyperoxic breathing from 21% to 55% oxygen independent of any change in leg $\text{VO}_{2\text{max}}$ ²⁰. Future studies manipulating RCV, and the partial pressure of arterial oxygen (PaO_2), while maintaining CaO_2 will help to clarify the rate limiting mechanism(s) of maximal exercise in various environments. The limited evidence suggests that diffusion limitations at the level of the skeletal muscle, even at sea level, may be greater than previously assumed, though they are easily overshadowed by convective limitations of oxygen transport.

While convective limitations in oxygen delivery have dominated scientific dogma in regards to

our understanding of a physiologic bottleneck limiting exercise capacity, it is important to acknowledge and identify diffusive limitations of oxygen flux that occur as well. For instance, in some fit to elite athletes a pulmonary limitation exists during exercise at sea level²¹⁻²³. Ventilation-perfusion inequality and alveolar-end-capillary oxygen diffusion limitation increase along with exercise intensity²⁴⁻²⁶ resulting in exercise-induced arterial hypoxemia (EIAH). EIAH is defined as a drop in arterial oxygen saturation (SaO₂) ranging from 95% (mild) to less than 88% (severe)^{27, 28}. The degree of EIAH positively correlates with training status and has been observed at both maximal²⁹ and submaximal exercise intensities^{22, 23}. Individuals that display EIAH during sea level exercise exhibit a more profound reduction in VO_{2max} at elevations above sea level that is apparent even when going to a low altitude of 1,000 m. Conversely, individuals that maintain SaO₂ during maximal exertion at sea level experience negligible decrements in VO_{2max} with an equivalent 1,000 m increase in elevation³⁰.

Hitherto, the principal factors limiting the maximal capacity for exercise at sea level has largely been attributed to the convective limitations of oxygen transport as opposed to the diffusive limitations at any point from the environment to the mitochondria, namely the lung and skeletal muscle^{16, 31-33}. This concept has been tested and challenged in regards to exercise performance at higher elevations.

Optimal hematocrit for exercise performance

The rheological properties of blood throughout the vascular network are not static and fluctuate according to vessel diameter. Htc and viscosity both decrease with diminishing vessel diameter, known as Fahraeus effect³⁴ and the Fahraeus–Lindqvist effect³⁵, respectively. Accordingly,

capillary Htc is significantly lower than systemic Htc ³⁶. An additional mechanism responsible for Htc heterogeneity in the microcirculation is the unequal division of red cell and plasma volumes at arterial bifurcations. This uneven separation, referred to as plasma skimming, with the daughter branch receiving a greater proportion of blood flow, also results in a disproportionately high distribution of erythrocytes ³⁷⁻³⁹. How these phenomena influence oxygen diffusion at the tissue, especially at moderate to high altitude, is unknown. Discussion of blood characteristics in this review refer to those measured in relatively large systemic vessels.

The optimal Htc for exercise performance is the Htc at which exercise capacity is maximized. Near sea level the optimal Htc has been proposed to occur when $\dot{V}O_2$ and cardiac output are collectively the greatest ⁴⁰⁻⁴³. The first study to ascertain an actual optimal Htc for both sea level $\dot{V}O_{2max}$ and endurance capacities (time to exhaustion; TTE) *in vivo* established that the relationship between the exercise capacity and Htc in a mouse model is parabolic ⁴⁴; exercise capacity improves with increasing Htc to a point where further increases begin to hinder maximal exercise capabilities (Fig. 1) due to increasing viscosity of the blood. The optimal Htc for maximal performance was observed at 57 and 68 % depending on acute or chronic presence of EPO in the animal's circulation ⁴⁴.

At higher elevations (i.e. 3,800 m), optimal Htc is theorized to occur as the mixed venous partial pressure of oxygen (PvO_2), in respect to Hb concentration ($[Hb]$), is maximized ⁴⁵. At an elevation of 4,724 m, heart rate of subjects was shown to decrease as Htc increased from 46 to 59%, and then reciprocally increase as Htc subsequently fell during stable submaximal exercise with the lowest submaximal heart rate occurring at Htc of 59%. While these observations were

indicative that increased Htc improved submaximal exercise performance, the value of 59% was never confirmed as an optimal Htc⁴⁶. The theoretical constructs of an optimal Htc for exercise performance has been discussed in the past^{7, 20, 40-42, 45, 47, 48} although this had never been directly measured in humans.

During exercise Htc may increase. Exercise induced hemoconcentration in humans occurs primarily from a transient shift of fluid from intravascular to extravascular compartments concomitant to increased blood flow, capillary perfusion, and increased filtration of both cutaneous and muscle capillary beds⁴⁹, but also to the slight contribution of erythrocytes from adrenergic stimulated splenic contraction^{50, 51}, and fluid loss through sweat with prolonged exercise. Unlike athletically endowed animals, such as the dog and horse, who can increase Htc (25-50%) during exercise by splenic contraction, thus allowing for an increase in $\text{VO}_{2\text{max}}$ (10-30%)⁵², exercise induced hemoconcentration in humans is small but significant with Htc increasing around 4-6%^{50, 51}, and both arterial [Hb] and oxygen carrying capacity improving by approximately 10%^{53, 54}. As mentioned above, the optimal Htc for maximizing exercise performance near sea level was found to be approximately 58% in ESA-treated wild type mice⁴⁴. Whether or not this value is transferable to humans is unknown, but this Htc far exceeds normal Htc in healthy male/females at rest (40-45% / 37-42%) and during exercise (45-50%/42-47%).

One past gold medal winning Olympic athlete possessed an autosomal dominant mutation in the EPO receptor that led to increased sensitivity of erythroid progenitors to EPO, and constitutively elevated [Hb] (231 g/l) and a Htc (68%) similar to the optimal Htc detected in mice that

constitutively overexpress EPO. This athlete displayed an exceptional aptitude for exercise together with such hematological parameters⁵⁵. This heightened [Hb] corresponds to an estimated CaO₂ at sea level of 30 ml of oxygen per dl of blood oppose to the approximate 20 ml/dl given that this athlete possessed a more common value of [Hb], 15 dl/ml, which precipitates roughly a 67% increase in locomotor oxygen delivery during exercise.

Apart from genetic disorders, the optimal Htc for exercise in mice at sea level is much closer to the Htc following acclimatization to high altitude that, dependent on elevation, can reach values ranging from 50-55% or above^{20, 56-59}. Nevertheless, the extent to which increases in RCV and, more importantly, the attendant increases in CaO₂ have on exercise performance at varying degrees of altitude above sea level still remains unclear.

Acclimatization and RCV

Although hypoxia-induced erythropoiesis is highlighted in this discussion, it is important to keep in mind that acclimatization to elevations ranging from low to extreme altitude is an exceptionally complex and integrative process of which is still being studied. In addition to erythropoiesis^{59, 60}, acclimatization includes, but is not limited to, alteration in ventilation and gas exchange⁶¹⁻⁶⁵, cardiovascular and hemodynamic function^{66, 67}, autonomic outflow^{68, 69} skeletal muscle morphology and biochemical expression⁷⁰⁻⁷⁵, neuroendocrine regulation⁷⁶, and nutrient partitioning⁷⁷. All these observable changes following acclimatization collectively modify physiologic homeostasis as well as one's capacity for exercise. Accordingly, the aim of this review is to provide new insights into the role of RCV on performance at moderate to high altitude and the underlying mechanism(s) attributable to the measured outcomes. This is

important seeing as how the relevant studies summarized in this review have utilized hypobaric hypoxia⁴⁶, acute hypoxic breathing^{15, 16, 40, 47, 78, 79}, and experimentation at actual altitude^{20, 56-58, 80-83}; the majority of studies investigate different severities and lengths of exposure to the respective altitude or degree of hypoxia which, very understandably, lead to different physiologic affects.

Acclimatization is commonly associated with an increase in RCV although not all high altitude dwelling mammals express this phenotype. Measurements in high altitude dwelling animals, such as the llama⁸⁴, and high altitude natives including the Tibetans⁸⁵ and Ethiopians⁸⁶, all showing values of total Hb mass and Htc that are closer to values observed in lowlanders at sea level, have led some to question the importance of hypoxia-induced erythropoiesis^{20, 56}. The llama's RCV is more elliptical than disc-shaped resulting in more viscous whole blood at a given Htc⁴¹. For this reason high altitude dwelling llamas understandably have lower Htc when compared to humans residing at the same elevation. Differences in Htc between high altitude native populations are not so clearly understood.

Discordantly to both Ethiopians and Tibetans, Andean natives express a Htc significantly above sea level values^{62, 85, 87, 88}. Recent evidence reveals that the gene encoding for hypoxia-inducible factor 2 alpha (HIF-2 α), EPAS-1⁸⁹, represents a key gene mutation explaining some of the differences to adapting and living at high altitudes among different native populations⁹⁰⁻⁹³. Tibetan and Andean natives exhibit similar maximal exercise capacities at 3,900 m despite significantly greater CaO₂, [Hb], and Htc in the Andean population⁹⁴. The maintenance of exercise capacity despite different hematological parameters may be explained by the gene

mutation in HIF-2 α observed in Tibetans⁹⁰⁻⁹³. It has been speculated that EPO-induced erythropoiesis has not evolved to cope with high altitude exposure, but to keep a balanced red blood cell production at or near sea level. Consequently it has been suggested that most humans are designed to live at or near sea level⁹⁵.

Comparisons of rheological properties between high altitude populations have not been examined. The influence of hypoxia on the biophysical properties of erythrocytes and whole blood is unclear. Hypoxia influenced hemorheological adaptations differ between species⁹⁶⁻⁹⁸ as well as within species⁹⁸⁻¹⁰². It appears that animals and humans susceptible to the development of high altitude illness have a more pronounced response (i.e., increase in blood viscosity and/or loss of erythrocyte deformability)^{98, 99, 101, 102}. Accordingly, a complete examination into differences in hemorheological compensation between Tibetans, Ethiopians, and Andeans is merited.

Aside from intergenetic variability between native high-altitude populations, the majority of humans experience some degree of erythropoietic activation when exposed to a hypoxic environment⁵⁹. This expansion in RCV occurs slowly over time in lowlanders sojourning to high altitude. As the availability of oxygen decreases, humans undergo an increase RCV through activation of erythropoietic precursor cells in bone marrow via EPO¹⁰³, which is primarily expressed by the kidneys. As our understanding of the mechanisms that upregulate EPO, mediated by HIF-2 α ^{104, 105}, has improved, the physiologic significance for this increase in RCV remains incomplete.

What is the relationship between RCV and exercise from low to high altitudes?

The general concept of improving the capacity for exercise at altitude via an increase RCV is simple. Exercise performance declines linearly from approximately 300 m to 3,000 m¹⁰⁶ with an average decline in $\text{VO}_{2\text{max}}$ of 6.4% for every 750 m^{80, 106, 107}. The loss of exercise capacity is even greater at elevations of 3000 m and above¹⁰⁸. Maximal sea level exercise capacity is directly related to CaO_2 ¹⁴. Thus it seems quite plausible to hypothesize that the loss of exercise capacity at altitude could be offset if CaO_2 was increased via an infusion or up-regulation of RCV. Clearly this supposition is not entirely true. While several studies have demonstrated a benefit of higher total Hb mass and Htc on an individual's capacity for exercise at elevations above 2,000 m^{16, 40, 46, 47, 57, 58, 83}, others have reported negligible effects^{16, 20, 56, 78, 80, 81}. These studies will be discussed below in more detail. Theoretical computation estimated the value of [Hb] and Htc to be between 15 - 18 g/dl and 45 - 54%, respectively, in order to optimize CaO_2 and oxygen utilization at an elevation of 3,800 m⁴⁵. An optimal Htc in humans or animals has never been directly determined at elevations above 500 m.

Published findings relating the change in exercise capacity following acclimatization to elevations above 2,000 m have been seemingly inconsistent. When comparing exercise capacity at elevations above sea level, both before and then following acclimatization, $\text{VO}_{2\text{max}}$ has been shown to increase at 2,300 m^{109, 110}, 3,800 m¹¹¹, and 4,300 m⁵⁷, but not after acclimatization to 3,475 m¹¹², 4,100 m^{113, 114}, and 4,300 m^{77, 115, 116}. Regardless, if exercise capacity does improve pre to post acclimatization, it never returns to sea level values^{82, 117, 118}.

Acclimatization and maximal exercise capacity at moderate to high altitudes

The following studies have specifically monitored changes in Htc, [Hb], and/or CaO₂ in parallel with an evaluation of exercise over time, while remaining at a respective altitude. Table 1 summarizes the data from such studies that have investigated changes in Htc, [Hb], and/or CaO₂ alongside measurements of exercise capacity comparing an initial/early versus a more chronic exposure to a particular elevation. Some studies have demonstrated a benefit to exercise capacity following acclimatization. Four weeks at 2,270 m increased Htc by 7.2% and absolute VO_{2max} by 5.6% above values collected 2 days after exposure to this moderate altitude¹¹⁹. When comparing 1 versus 16 days acclimatization to 4,300 m, Htc, CaO₂, and relative VO_{2max} increased by 12.7%, 18.5%, and 9.9%, respectively⁵⁷. Additionally, VO_{2max} increased subsequent to acclimatization at 4,300 m despite no change in maximal cardiac output⁵⁷. When Htc and CaO₂ were then lowered by 10.6% and 8.8%, respectively, via isovolemic hemodilution, VO_{2max} was also reduced by 8.2%⁵⁷. When compared to acute hypoxic exposure, lowland natives acclimatized to 5,260 m demonstrated a 31.3% increase in CaO₂ attendant to a 30.4% increase in [Hb] both of which corresponded to a 13% increase in absolute VO_{2max}⁸³.

With the uncertainty concerning RCV, exercise capacity, and well being at higher elevations, the identification of a “normal” Htc value in high-altitude natives was sought. Subjects volunteering for this study were residents of and around La Paz, Bolivia (approximately 3,700 m), and were classified as anemic, normal, or polycythemic dependent upon Htc which averaged to be 42%, 54%, and 65%, respectively⁵⁸. Exercise tests were administered to normal and anemic subjects. The 28.6% higher average Htc in normal subjects corresponded to a 26.9% greater average absolute VO_{2max} versus anemic subjects⁵⁸. Unfortunately the exercise capacity for those that presented with polycythemia could not be measured.

Certain sporting events, such as the 1968 summer Olympics in Mexico City, are held at moderate to high altitudes. Exercise or sport performance that require repetitive and strenuous skeletal muscle contraction lasting two minutes or more are hindered by a limitation in oxygen availability^{120, 121}. Spending time at the respective elevation prior to competition helps to minimize a decrement in performance. Two to three weeks at 2,300 m improved long distance running and swimming performance at moderate altitude¹¹⁰. Contrarily, too much time spent at high elevations may consequently diminish overall exercise performance¹²¹. Thus, Schuler *et al.* (2007) examined the minimum time at moderate altitude necessary to maximize exercise performance. The most dramatic increases in exercise performance ($\text{VO}_{2\text{max}}$, maximal power output, and time-to-exhaustion (TTE)) occurred following 14 days at 2,340 m. Additionally, all facets of exercise improvement strongly correlated with the measured changes in Htc and CaO_2 . When compared to the first day of arrival, a 10.4% increase in Htc and 11.5% improvement in CaO_2 associated with an increases in absolute $\text{VO}_{2\text{max}}$ (8.2%; Fig. 2A), maximal power output (8.9%; Fig 2B), and TTE (12.0%; Fig. 2C)⁸², all of which suggest a benefit of an increase Htc and oxygen carrying capacity on exercise performance at moderate altitude.

Other studies failed to verify an improvement in exercise capacity following acclimatization and change in RCV. Compared to acute hypoxic exposure, 15 to 17 days at 4,300 m led to an increase of [Hb] by 20.3% and CaO_2 by 29.2%, but failed to increase $\text{VO}_{2\text{max}}$ ¹²². Three weeks at 5,200 m increased both Htc and [Hb], but did not improve relative $\text{VO}_{2\text{max}}$ values (non-significant increase of 4.1%)¹²³. Unexpectedly, however, when Htc was then decreased by 2.3% via oral administration of an isomolar solution, $\text{VO}_{2\text{max}}$ significantly decreased by 7.3%¹²³. At

5,050 m, when comparing one week to five weeks of altitude exposure, an 8.0% increase in [Hb] corresponded to a non-significant increase in absolute $\text{VO}_{2\text{max}}$ of 13.2%¹²⁴. Lastly, despite an 11.3% larger total Hb mass following 6 months of intermittent acclimatization to 3500 m, no differences in high altitude $\text{VO}_{2\text{max}}$ were observed when comparing lowland controls to subjects exposed to intermittent hypoxic¹²⁵.

Acclimatization of lowlanders to a respective elevation was thought to lessen the loss of $\text{VO}_{2\text{max}}$ to values above those obtained during acute hypoxic exposure¹²⁶. Summarization of the literature fails to verify this belief, however, the loss of exercise capacity as well as the ability to improve following acclimatization appears to be dependent upon the elevation. Other studies have manipulated RCV directly, either in the presence or absence of acclimatization, while also monitoring the attendant changes to exercise capacity.

Artificial manipulation of RCV and maximal exercise capacity at moderate to high altitude

Examining the role of RCV on exercise capacity at altitude has also been studied by direct manipulation. Decreasing RCV through the means of hemodilution, as was previously mentioned^{57, 123}, and/or increasing RCV through various means aside from natural acclimatization such as direct infusion of blood^{40, 47, 80}, or by administration of an ESA^{16, 78} have all been examined. The effect on exercise capacity at altitude following either a decrease or an increase in RCV will be presented categorically dependant upon means of RCV augmentation.

Hemodilution and maximal exercise capacity

To emphasize the uncertainties regarding the role of RCV on exercise capacity at altitude,

several studies have examined changes to exercise capacity at altitude following hemodilution. The basis for such experiments was derived from the difference between the theoretical estimation of 47% as the optimal Htc for human blood⁴¹ opposed to Htc values actually measured in both high-altitude natives (Aymara) and lowlanders acclimatized to high altitudes which are typically greater than 50%^{20, 56-58}. It is hypothesized that for some given Htc the associated blood viscosity will negate any benefit of enhanced CaO_2 due a loss of cardiac capacity^{41, 43} though such a value has never been identified. Transgenic mice that constitutively overexpress EPO (Tg6) and present with high Htc, 75 to 91%, adapt several mechanisms helping to maintain normal function despite excessive erythropoiesis and attendant blood viscosity. These mechanisms include increased erythrocyte flexibility and increased plasma nitric oxide synthase levels¹²⁷⁻¹³⁰. Whether or not humans display similar adaptations with high Htc is unknown. Since an optimal Htc for exercise at different elevations has yet to be identified, some studies have examined the effect of increasing RCV, while others have attempted the opposite and decreased an already elevated RCV. Table 2 summarizes the results of such studies.

Hemodilution in one polycythemic subject at 4,250 m decreased Htc from 62 to 42% (Δ -32.3%)⁵⁶. Though $\text{VO}_{2\text{max}}$ was not reported, isovolemic hemodilution increased heart rate, stroke volume, cardiac output, breathing frequency, VO_2 , and respiratory exchange ratio at an absolute workload of 49 W⁵⁶; each change suggestive of a loss in exercise capacity. The authors suggested otherwise by stating that the ventilatory breakpoint improved following hemodilution supporting the idea that a decline in RCV improved exercise performance at 4,250 m⁵⁶. The diffusive capacity of oxygen in skeletal muscle (DmO_2) in hypoxia (fraction of inspired oxygen, FiO_2 , of 12%) was later examined following isovolemic hemodilution. The replacement of 526

ml of blood with saline effectively reduced [Hb] and CaO₂ by 13.2% and 8.8%, respectively⁷⁹. These reductions resulted in a loss of VO_{2max} of approximately 13.5% in addition to a decrease in DmO₂⁷⁹. The capacity to perform dynamic two-legged knee extensor exercise was examined after decreasing Htc (20.9%) and CaO₂ (18.9%) during hypoxic (FiO₂ of 11%) exercise. Peak VO₂ values diminished by 19.4%¹⁵. The correlation between limb blood flow and CaO₂ was significant (r = 0.99), whereas the relationship between blood flow and PaO₂ was not¹⁵. One liter of blood replaced with Dextran 70 following 9 weeks of acclimatization to 5,260 m²⁰ decreased both Htc (25.0%) and CaO₂ (23.2%) with no change in VO_{2max}²⁰.

Blood viscosity has an important role in hemodynamic control and though blood viscosity was not measured in the latter study, nor any other studies mentioned in this section, an increase in plasma viscosity by means of viscogenic plasma expanders may help to maintain vasomotor tone and microvascular function despite reductions in oxygen delivery¹³¹. This can play a part as to why VO_{2max} failed to decrease following a loss of oxygen carrying capacity at high altitude.

Blood transfusions and maximal exercise capacity

Summarized results for studies examining the effect of RCV infusion on exercise capacity at elevations above sea level are illustrated in Table 3. Initial studies reported a positive affect of RCV manipulation through acute infusions. In 1945, Lieutenant Pace and colleagues⁴⁶ pioneered the first study that examined the effect of RCV manipulation and the response on exercise capacity at 4,724 m using a hypobaric chamber. This classic study investigated the effect of a 3-4 day, 2,000 ml RCV transfusion (50% suspension) on heart rate during submaximal exercise performance at this simulated altitude. The transfusion of RCV significantly increased Htc and

CaO₂ by approximately 28% and 23%, respectively, which significantly lowered heart rates during submaximal exercise compared to those infused with an equal volume of saline. The authors suggested that an expansion in RCV via blood transfusion improves exercise tolerance in hypoxia⁴⁶. A blood infusion consisting of 525 ml of packed RCV increased Htc by 26.6% and improved VO_{2max} by 13.0% in subjects that were subjected to an acute bout of hypoxia (FiO₂ of 13.5%) simulating 3,566 m⁴⁷. Building upon initial findings, an autologous infusion of 334 ml of packed erythrocytes increased Htc by 17.8% and improved VO_{2max} by 10.2% in subjects that were also subjected to an acute bout of hypoxia (FiO₂ of 16%) simulating 2,255 m⁴⁰.

Later studies challenged such an effect. A blood infusion consisting of 295 ml of packed RCV significantly increased [Hb] by approximately 9% however failed to increase either CaO₂ or VO_{2max} within 10-14 hours of arriving at 4,300 m⁸⁰. The RCV infused subjects were reported to have an average VO_{2max} that was 230 ml/min above saline infused controls (reported as a trend, no p-value provided)⁸⁰.

Two possible explanations for these findings are: 1.) Out of three studies, the only one to suggest that RCV infusion doesn't increase exercise capacity at elevations above sea level infused the smallest amount of RCV, and was the only study to fail in improving CaO₂⁸⁰; or 2.) RCV infusion is effective in improving exercise capacity during acute hypoxic exposures simulating 3,566 and 2,255 m^{40, 47}, but not at higher elevations such as 4,300 m⁸⁰ because of a limitation in oxygen diffusion.

ESA and maximal exercise capacity

The most recent means of expanding RCV in attempt to improve exercise capacity at altitude consists of treatment with an ESA, which has ostensibly replaced the use of blood transfusions. The results of these studies are summarized on Table 4. It should be noted that the physiological effects of EPO extend beyond hematological parameters¹³². Whether a non-erythroid effect of EPO improves exercise capacity is currently under investigation. There is evidence however to suggest that near sea level the effects of both low dose, long term EPO administration on VO_{2max} is dependent solely on hematologic changes^{10, 133}, and that there is even a greater improvement of submaximal versus maximal exercise performance¹¹.

The principle study to have examined the effect of RCV manipulation via an ESA on exercise performance in acute hypoxia (FiO_2 of 12.4%) used weekly subcutaneous injections of novel erythropoiesis stimulating protein (NESP), which increased Htc and CaO_2 by 16.7% and 11.6%, respectively⁷⁸. Despite increases to both Htc and CaO_2 , VO_{2max} was not affected ($\Delta 0\%$) at the simulated elevation of 4,100 m,⁷⁸.

The first and only study to analyze the effect of equivalent changes in RCV on exercise capacity when exposed to different degrees of hypoxia also used ESA for RCV manipulation¹⁶. The results of the study are summarized in Table 5. Briefly, 5 weeks of treatment with recombinant human erythropoietin (rhEpo) increased Htc across 4 separate hypoxic exposures (FiO_2 : 17.4, 15.3, 13.4 and 11.5% simulating 1,500, 2,500, 3,500, 4,500 m, respectively) during maximal exercise, whereas CaO_2 and VO_{2max} increased in all hypoxic exposures except for the lowest oxygen concentration, 11.5%¹⁶.

Taken together, all the studies that utilized acute manipulations of RCV indicate that from 1,500 m to somewhere between 3,500 and 4,500 m greater RCV improve $\text{VO}_{2\text{max}}$ during acute exposure to hypoxia. At some point, however, between elevations of 3,500 and 4,500 m, any assistance to exercise capacity via greater RCV is seemingly lost.

Exercise capacity at moderate to high altitude with changes in blood and plasma volume

Total blood volume is comprised predominantly of RCV and plasma volume. Though this review focuses on the effect of RCV changes on exercise capacity at moderate to high altitudes, plasma volume also changes at such elevations and merits reference. Ascent to higher elevations incurs a fairly rapid (4 hours) loss of plasma volume ($\approx 20\%$) that persists while at altitude^{59, 118, 134-138}. The loss results, at least transiently, in a reduction in total blood volume. Hypoxic ventilatory drive increases respiration, and ultimately reduces plasma volume. Insensible water loss increases linearly with ventilation as does excess carbon dioxide expiration, alkalosis, which is then offset by renal bicarbonate excretion, and diuresis¹³⁹. The loss of plasma assists with hemoconcentration of the blood so Htc increases independent from erythropoiesis (of which increases RCV population over several weeks). This plasma loss partially accounts for the initial weight loss and the drop in cardiac filling pressures of the heart at altitude^{140, 141}, but has little if any effect on maximal exercise capacity¹⁴².

After 9 weeks of acclimatization to 5,260 m, plasma and total blood volume were decreased from sea level values, and though an infusion of 1 liter 6% dextran increased total blood volume from an average of 5.40 to 6.32 liters, maximal exercise capacity failed to improve at high altitude when compared to preinfusion values¹¹⁸. Alternatively, after approximately 18 days of

exposure to high/extreme altitude (7 days at 4,350 m followed by 10-12 days at a simulated 6,000 m), resting plasma volume, but not total blood volume ($p = 0.06$), was decreased from sea level values by 25.8% (3.68 ± 0.51 liters at sea level to 2.73 ± 0.63 liters at altitude) and an infusion of 219 \pm 22 ml of Hesteril 6% improved maximal exercise capacity by 9% while at 6,000 m¹³⁸.

Supplemental carbon dioxide (3.77% CO₂) during 5 days of simulated hypobaric hypoxia prevented hemoconcentration and maintained body weight suggesting the maintenance of plasma volumes¹⁴³. Despite maintenance of plasma volume, exercise capacity still diminished by 33% (3.1 to 2.08 l/min), which was even more than the 29% decrease in subjects exposed to just hypobaric hypoxia without supplemental carbon dioxide (3.19 to 2.26 l/min)¹⁴³. There was a greater loss of exercise capacity despite no detected loss of stroke volume in the subjects supplemented with carbon dioxide, while it decreased in those without supplementation¹⁴³. Arterial oxygen tension was the only variable significantly different between the two groups, and served as the best explanation for the differences in exercise capacity highlighting the importance of PaO₂ on the rate of oxygen diffusion and exercise capacity in hypoxic conditions.

The indifference of plasma volume on exercise capacity at increasing altitudes is clear, as plasma volume expansion fails to consistently improve exercise capacity or maximal cardiac output at moderate to extreme altitude^{118, 135, 138} when acute supplementation of 50-100% O₂ restores maximal heart rate¹⁴⁴, work capacity^{144, 145}, maximal power output, and leg VO₂^{20, 118} to near sea level values independent from changes in plasma or total blood volume. This also

emphasizes the importance of oxygen tension and carrying capacity on exercise performance at moderate to high altitude.

Convective versus diffusive limitations of oxygen transport during exercise at elevations above sea level

The principal limitation to exercise capacity near sea level is understood to be primarily a result of the convective restraints in oxygen transport such as cardiac output and CaO_2 ^{31, 54, 146}. The improvement in exercise capacity at sea level following an increase in RCV, and more importantly CaO_2 , becomes less prominent as elevation increases. As elevation increases, the primary limiting factor of exercise capacity shifts to an insufficient oxygen gradient in which the ability to drive oxygen diffusion progressively diminishes, i.e., a loss of driving pressure or a diffusive limitation to oxygen transport, occurring particularly in the lung and skeletal muscle¹⁴⁷. A pressure gradient is the driving force that facilitates oxygen diffusion from the environment to the lungs, the lungs to circulating Hb within the RCV, and finally from Hb to the metabolic machinery of the cell. The loss of environmental or ambient oxygen pressure results in the decrement of driving pressure throughout the entire cascade of oxygen transport.

By ascending to elevations above sea level, the progressive decrease in pressure gradient reduces the rate of oxygen diffusion, ultimately limiting oxygen flux and constraining maximal cellular respiration capacities. At high to extreme altitudes, the diffusive limitations of oxygen offset any increase in oxygen carrying capacity via erythrocyte infusion, EPO administration, or even acclimatization. Opposingly, and further underscoring the limitation in pressure gradient at high to extreme altitude, restoring arterial oxygen tension to sea level values reestablishes maximal

power output and maximal leg VO_2 values to those observed at sea level²⁰.

The phenomenon where the driving pressures of oxygen diffusion becomes limiting, which then alters exercise performance, is referred to as the “*critical PO_2* ”. More specifically, the critical PO_2 is the theoretical value of arterial oxygen tension where maximal oxygen diffusion becomes restricted and results in a loss of exercise capacity. The critical PO_2 for maximal and submaximal exercise performance appear to differ^{148, 149} though identification of an actual critical PO_2 is lacking. The value has been estimated to occur somewhere from 3,500 m to elevations above 4,000 m^{16, 78, 150}, elevations that result in PaO_2 value less than or equal to 40 mmHg¹⁵¹, or at elevations where SaO_2 fall to a value ranging from 70 to 75% and below¹⁵².

Diminishing PO_2 concomitant to increasing elevations results in increased diffusion limitations that are particularly apparent in the lung^{144, 153-156}, skeletal muscle^{114, 154, 157}, and though not yet directly measured, is suggested to play a larger role on central nervous system (CNS) oxygenation at high to extreme altitudes, more so than the loss of CaO_2 ¹⁵². A loss of exercise capacity in hypoxia may be explained by a change in fatigue pattern from peripheral to central mechanisms¹⁵⁸. The transport of oxygen from the environment to the mitochondria is dependent upon both the capacity to carry oxygen to the metabolically active tissue as well as the pressure difference to facilitate diffusion to the respiring organelle. Maximal oxidative phosphorylation capacity of the vastus lateralis in highly trained cyclists was identified as the strongest determinant of exercise performance at 1,020 m¹⁵⁹. At moderate to high altitudes, an increase in RCV enhances the total capacity to carry oxygen but its effects on the rate of oxygen diffusion to respiring cells are small to negligible¹⁵⁷. At altitudes corresponding to or above the critical PO_2 ,

the declining partial pressure of oxygen results in diffusion limitations from the environment into the body, e.g., pulmonary, as well as with oxygen unloading to tissues throughout the body, independent of increases in CaO_2 , and thus limiting maximal oxygen capacity^{119, 139, 154}.

Exercise itself exacerbates altitude-induced hypoxemia, as alveolar to arterial PO_2 difference (A-aDO_2) is linearly related to exercise intensity. Arterial hypoxemia is primarily attributed to an excessive exercise-induced widening of the A-aDO_2 in which the hyperventilatory response fails to sufficiently compensate. The effect of the exercise-induced widening of A-aDO_2 becomes more prominent as elevation increases.²³ Exercise-induced A-aDO_2 widening strains systemic buffering capacity, as bicarbonate supplementation abates EIAH¹⁶⁰. Exercise in combination with the loss of ambient oxygen tension at higher altitudes worsens the limitations of oxygen diffusion in the lungs, lowering PaO_2 , reducing SaO_2 as well as attendant CaO_2 , and ultimately attenuating oxygen delivery to all tissue. Overall the loss of diffusion gradient at the critical PO_2 counteract those attributed to a greater convective transport of oxygen, such as greater CaO_2 , resulting in negligible changes in maximal exercise capacity¹³⁹.

Diffusion limitations help to explain the seemingly paradoxical effect of a diminished exercise capacity following acclimatization to high altitudes despite large increases RCV and attendant CaO_2 that exceed values measured at sea level²⁰. Not one study that utilized acute means of RCV manipulation demonstrated an increase in $\text{VO}_{2\text{max}}$ following an increase in RCV above elevations of 3,600 m^{16, 78, 80}.

Studies that examined acclimatization as means of increasing RCV and changes in exercise

capacity differ from the studies that utilized acute methods of RCV manipulation. Above elevations of 3,600 m, increases in RCV sometimes correlated to an improvement in $\text{VO}_{2\text{max}}$ ^{57, 58, 83} and other times did not¹²²⁻¹²⁴. The critical PO_2 is undoubtedly a dynamic rather than static phenomenon and fluctuates with acclimatization. Diffusive capacity of oxygen does appear to improve following acclimatization⁶⁵ as shown by improvements in PaO_2 and SaO_2 ^{83, 115}, smaller A-a DO_2 gradient^{83, 161, 162}, greater arteriovenous oxygen difference (a-v O_2)^{83, 122}, and an improved ratio of minute ventilation (V_E) to VO_2 at a given workload⁶².

The seemingly inconsistent correlations between RCV and $\text{VO}_{2\text{max}}$ following acclimatization may also be attributed to “noise” associated with different tests of maximal exercise used across studies (Table 1). Individual values of $\text{VO}_{2\text{max}}$ fluctuate according to subject characteristics such as degree of acclimatization to the respective elevation, training status, body mass, body composition, age and gender¹⁶³. In well-trained subjects, the loss of $\text{VO}_{2\text{max}}$ when subjected to the same absolute increase in elevation exhibits a broad inter-individual variability^{30, 106}. Level of training varied greatly among subjects across studies (Table 1). None of the studies provided data detailing subject training or activity level while exposed to their respective elevations. The studies that monitored changes in Htc, [Hb], and/or CaO_2 alongside exercise performance while remaining at a specific altitude (extending from 2,270 to 5,260 m) used varying spans of time (ranging from 2 to 10 weeks) (Table 1). The possibility of confounding factors due to training or detraining adaptations should be considered with these results and accounted for in future studies.

In general, the data suggests that at elevations in which the critical PO_2 has not been met, maximal exercise is primarily limited via properties of oxygen convection, and an increase in CaO_2 would correlate with concomitant improvements in maximal exercise capacity. One of the most common mechanisms used to increase CaO_2 , and the most viable for enhancing exercise, is by increasing RCV.

Conclusions

This review elucidates the role of RCV on performance at altitude and the underlying mechanism(s) attributable to the measured outcomes. At 500 to 3,500 m, convective limitations in oxygen transport primarily govern maximal exercise capacity, and increases in RCV and CaO_2 result in greater VO_{2max} . Alternatively at 4,500 m and higher, the decrease in the partial pressure gradient of oxygen attendant to an increasing elevation leads to a loss of both driving pressure and rate of oxygen diffusion at the lung as well as the metabolic tissue, ultimately limiting oxygen consumption and VO_{2max} . At high to extreme altitudes, RCV and any attendant increases in CaO_2 have less influence on exercise capacity when compared to lower elevations. This explains the seemingly paradoxical findings of how RCV and VO_{2max} do not correlate at elevations ranging from high(er) to extreme altitudes (approximately 3,500 to 4,500 m and above). In between 3,500 to 4,500 m exists a critical PO_2 ; a theoretical value of arterial oxygen tension where maximal oxygen diffusion becomes restricted resulting in a loss of exercise capacity. The critical PO_2 is dependent upon acclimatization, gender, and individual training status. Future research shall attempt to elucidate limitations in oxygen transport and pinpoint a critical PO_2 by manipulating RCV and PaO_2 , while maintaining CaO_2 , to explain oxygen flux limitations during maximal exercise in various environments.

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982 **Table 1**

Study	Sample size	Elevation (or simulated elevation)	Method of RCV Manipulation	Method of Maximal Exercise Test	Method of Endurance Test	Δ Htc	Δ [Hb] (g/dl)	Δ CaO ₂ (ml/dl)	Δ WB VO _{2max}	Δ Endurance Capacity
Pugh, 1967	n = 6	4 weeks at 2,270 m	Natural acclimatization	Incremental series of exercise in 5 min blocks	Running time trials: 4.8 and 1.6 km	0.444 to 0.476 ↑ 7.2%	Not reported	Not reported	3.23 to 3.41 l·min ⁻¹ ↑ 5.6%	↑ 2.6% (23 sec) for 4.8 km, ↑ 1.8% (4.9 sec) for 1.6 km
Horstman <i>et al.</i> , 1980	n = 9	15 to 16 days exposure at 4,300 m	Natural acclimatization	Series of 4 brief incremental treadmill tests	Time until fatigue at 86% hypoxic VO _{2max}	0.479 to 0.540 ↑ 12.7%	Not reported	16.8 to 19.9 ↑ 18.5%	35.3 to 38.8 ml·kg ⁻¹ ·min ⁻¹ ↑ 9.9%	51.1 to 81.4 min ↑ 59.3%
Tufts <i>et al.</i> , 1985	Anemic: n = 10 Non-anemic: n = 46	Native of 3,700 m	High-altitude native – long term adaptation	Modified Balke cycle ergometer protocol	None	0.42 vs 0.54 ↑ 28.6%	13.6 vs 18.9 ↑ 39.0%	Not reported	2.12 vs 2.69 l·min ⁻¹ ↑ 26.9%	N/A
Bender <i>et al.</i> , 1988	n = 7	15 to 17 days exposure at 4,300 m	Natural acclimatization	Incremental cycle ergometer protocol	3-5 minutes at 43, 70, and 95% normoxic VO _{2max}	Not reported	14.3 to 17.2 ↑ 20.3%	16.1 to 20.8 ↑ 29.2%	2.52 to 2.49 l·min ⁻¹ ↓ 1.2% NS	↑ a-v O ₂ , ↑ PaO ₂ , ↑ SaO ₂ , ↓ LBF, ↔ O ₂ delivery
Boutellier <i>et al.</i> , 1990	n = 6	3 weeks at 5,200 m	Natural acclimatization	Extrapolation via HR/VO ₂ relationship & HR _{max}	None	Approx 0.501 to 0.556 ↑ 10.9%	16.4 to 18.2 ↑ 11.0%	Not reported	36.9 to 38.4 ml·kg ⁻¹ ·min ⁻¹ ↑ 4.1% NS	N/A
Grassi <i>et al.</i> , 1996	n = 10	1 week vs. 5 weeks at 5,050 m	Natural acclimatization	Incremental cycle ergometer protocol	None	Not reported	17.4 to 18.8 ↑ 8.0%	Not reported	1.89 to 2.14 l·min ⁻¹ ↑ 13.2% NS	N/A
Calbet <i>et al.</i> , 2003b	n = 7 (3 female, 4 male)	9 to 10 weeks at 5,260 m	Natural acclimatization	Incremental cycle ergometer protocol	Constant load test between 102 to 140 W	Measured but not reported	13.8 to 18.0 ↑ 30.4%	16.6 to 21.8 ↑ 31.3%	2.12 to 2.4 l·min ⁻¹ ↑ 13.2%	↓ HR, ↑ a-v O ₂ , ↑ O ₂ delivery
Schuler <i>et al.</i> , 2007	n = 8	14 days exposure at 2,340 m	Natural acclimatization	Incremental cycle ergometer protocol	Constant load test at 80% normoxic VO _{2max}	0.404 to 0.446 ↑ 10.4%	13.1 to 14.6 ↑ 11.5%	16.5 to 18.4 ↑ 11.5%	4.25 to 4.60 l·min ⁻¹ ↑ 8.2%	31.66 to 35.46 min ↑ 12.0%
Prommer <i>et al.</i> , 2007	Sea Level: (n = 15) Intermittent Hypoxia: (n = 15)	SL: Sea level for 6 months, IH: Hypoxic– normoxic cycles of 11 days at 3,550 m and 3 days at sea level for 6 months	Natural acclimatization	Incremental cycle ergometer protocol at 3,550m	None	0.467 vs 0.487 ↑ 4.3% NS	Total Hb _{mass} (g) 751 vs 836 ↑ 11.3%	18.4 vs 20.2 ↑ 9.8%	42.5 vs 41.7 ml·kg ⁻¹ ·min ⁻¹ ↓ 1.9% NS	N/A

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985 **Table 2**

Study	Sample size	Elevation (or simulated elevation)	Method of RCV Manipulation	Method of Maximal Exercise Test	Method of Endurance Test	Δ Htc	Δ [Hb] (g/dl)	Δ CaO2 (ml/dl)	Δ WB VO _{2max}	Δ Endurance Capacity
Horstman <i>et al.</i> , 1980	n = 5	20-21 days exposure at 4,300 m	Isovolemic hemodilution	Series of 4 brief incremental treadmill tests	Time until fatigue at 86% hypoxia VO _{2max}	0.534 to 0.477 ↓ 10.6%	Not reported	19.3 to 17.6 ↓ 8.8%	39.2 to 36.0 ml·kg ⁻¹ ·min ⁻¹ ↓ 8.2%	90.2 to 58.8 min ↓ 34.8%
Winslow <i>et al.</i> , 1985	n = 1	Native of 4,250 m	Isovolemic hemodilution	Incremental cycle ergometer protocol	Constant load tests at 0 & 49 W	0.62 to 0.42 ↓ 32.3%	22.4 to 16.0 ↓ 28.6%	Not reported	↔ No change reported Values not given	↑ V _E , ↑ VO ₂ , ↑ HR, ↑ RER, ↑ Q
Boutellier <i>et al.</i> , 1990	n = 4	5 weeks at 5,200 m	Hemodilution via oral ingestion of isomolar solution	Extrapolation via HR/VO ₂ relationship & HR _{max}	None	Approx 0.556 to 0.543 ↓ 2.3%	Not reported	Not reported	38.2 to 35.4 ml·kg ⁻¹ ·min ⁻¹ ↓ 7.3%	N/A
Schaffartzik <i>et al.</i> , 1993	n = 7	Acute FiO ₂ : 12.0%; 4,300 m	Isovolemic hemodilution	Incremental cycle ergometer protocol	None	0.495 to not reported ↓ ?%	15.9 to 13.8 ↓ 13.2%	17.1 to 15.6 ↓ 8.8%	Leg VO _{2max} ; 0.96 to 0.83 l·min ⁻¹ ↓ 13.5%	N/A
Roach <i>et al.</i> , 1999	n = 7	Acute FiO ₂ : 11.0%; 5,000 m	Isovolemic hemodilution	Incremental knee-extensor contractions	None	Approx 0.43 to 0.34 ↓ 20.9%	Approx 14.3 to 11.5 ↓ 19.6%	Approx 16.4 to 13.3 ↓ 18.9%	2.11 to 1.70 l·min ⁻¹ ↓ 19.4%	N/A
Calbet <i>et al.</i> , 2002	n = 8	9 weeks at 5,260 m	Isovolemic hemodilution	Incremental cycle ergometer protocol	Constant load test at 120 W	0.52 to 0.39 ↓ 25%	18.5 to 14.2 ↓ 23.2%	22.2 to 17.1 ↓ 23.0%	Approx 2.48 to 2.40 l·min ⁻¹ ↓ 3.2%, NS	↑ HR, ↑ 2LBF, ↑ Q, ↑ SVC & LVC, ↓ MAP

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Study	Sample size	Elevation (or simulated elevation)	Method of RCV Manipulation	Method of Maximal Exercise Test	Method of Endurance Test	Δ Htc	Δ [Hb] (g/dl)	Δ CaO ₂ (ml/dl)	Δ WB VO _{2max}	Δ Endurance Capacity
Pace <i>et al.</i> , 1945	RBC Tx: n = 5 Saline Tx: n = 5	Intermittent hypobaric hypoxia 4,724 m	Blood infusion 2000 mL (50% RBC; 1000 ml)	None	Submaximal walking test	Approx 0.46 vs 0.59 ↑ 28.3%	Not reported	Approx 14.2 vs 17.5 ↑ 23.2%	N/A	Lower HR walking at submax intensity
Robertson <i>et al.</i> , 1982	n = 5	Acute FiO ₂ : 13.5%; 3,566 m	RBC reinfusion 750 ml (70% RBC; 525 ml)	Bruce multistage treadmill protocol	TTE @ 75% normoxic pre-infusion VO _{2max}	0.433 to 0.548 ↑ 26.6%	13.8 to 17.6 ↑ 27.5%	Not reported	2.62 to 2.96 l·min ⁻¹ ↑ 13.0%	687 to 748 sec ↑ 8.9%
Robertson <i>et al.</i> , 1984	n = 9	Acute FiO ₂ : 16.0% 2,255 m	RBC reinfusion 475 ml (70% RBC; 334 ml)	Multistage cycle ergometer protocol	Exercise at 70% normoxic pre-infusion VO _{2max}	0.381 to 0.449 ↑ 17.8%	12.7 to 14.7 ↑ 15.7%	Not reported	Approx 2.15 to 2.37 l·min ⁻¹ ↑ 10.2%	HR ↓ 12.2% [La] ↓ 27.4%
Young <i>et al.</i> , 1996 & Pandolf <i>et al.</i> , 1998	Control, n = 8; RBC infused, n = 8	1 to 3 days exposure at 4,300 m	RBC reinfusion 700 ml (42% RBC; 295 ml)	Incremental treadmill protocol	Time to complete 3.2 km run	Not reported	Approx 14.3 vs 15.6 ↑ 9.1%	Approx 16.7 vs 18.3 ↑ 9.6%, p = 0.55	3.11 vs 3.34 l·min ⁻¹ ↑ 7.4%, NS	1,184 vs. 1,142 sec ↓ 3.5%, NS

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Study	Sample size	Elevation (or simulated elevation)	Method of RCV Manipulation	Method of Maximal Exercise Test	Method of Endurance Test	Δ Htc*	Δ [Hb] (g/dl)*	Δ CaO2 (ml/dl)*	Δ WB VO _{2max} l·min ⁻¹	Δ Endurance Capacity
Lundby <i>et al.</i> , 2006	n = 10	Acute FiO ₂ : 12.4%; 4,100 m	4 weeks NESP treatment	Incremental cycle ergometer protocol	15 min submax; 100 W female, 150 W male	0.42 to 0.49 ↑ 16.7%	13.8 to 16.8 ↑ 21.7%	17.2 to 19.2 ↑ 11.6%	3.12 to 3.12 l·min ⁻¹ ↔ 0%, NS	↓[La] 18.4% ↓ RER 8.5%
Robach <i>et al.</i> , 2008	n = 7	Acute FiO ₂ : 17.4%; 1,500 m	5 weeks rhEpo treatment	Incremental cycle ergometer protocol	None	0.477 to 0.519 ↑ 8.8%	15.5 to 17.1 ↑ 10.3%	18.7 to 20.7 ↑ 10.7%	Approx ↑ 9.1%	N/A
Robach <i>et al.</i> , 2008	n = 7	Acute FiO ₂ : 15.3%; 2,500 m	5 weeks rhEpo treatment	Incremental cycle ergometer protocol	None	0.482 to 0.514 ↑ 6.6%	15.8 to 16.8 ↑ 6.3%	18.0 to 19.1 ↑ 6.1%	↑ 14.0%	N/A
Robach <i>et al.</i> , 2008	n = 7	Acute FiO ₂ : 13.4%; 3,500 m	5 weeks rhEpo treatment	Incremental cycle ergometer protocol	None	0.474 to 0.523 ↑ 10.3%	15.6 to 16.9 ↑ 8.3%	16.2 to 18.0 ↑ 11.1%	↑ 17.5%	N/A
Robach <i>et al.</i> , 2008	n = 7	Acute FiO ₂ : 11.5%; 4,500 m	5 weeks rhEpo treatment	Incremental cycle ergometer protocol	None	0.481 to 0.508 ↑ 5.6%	15.5 to 16.8 ↑ 8.4%	14.7 to 15.3 ↑ 4.1%, NS	↑ 1.9%, NS	N/A

1006 **Table 5**

Variable	% Δ at 1,500 m	% Δ at 2,500 m	% Δ at 3,500 m	% Δ at 4,500 m
Htc	↑ 8.8*	↑ 6.6*	↑ 10.3*	↑ 5.6*
CaO ₂	↑ 10.7*	↑ 6.1*	↑ 11.1*	↑ 4.1 ^{NS}
VO _{2max}	↑ 9.1*	↑ 14.0*	↑ 17.5*	↑ 1.9 ^{NS}

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Table Legends

Table 1. Summary of studies that have examined the effect of acclimatization on exercise capacity.

NS = not significant (unless specified, all data presented represents a significant change); RCV = red blood cell volume; Δ = change; Htc = percent Htc; [Hb] = Hb concentration; CaO_2 = arterial oxygen content; WB = whole body; $\text{VO}_{2\text{max}}$ = maximal oxygen consumption; N/A = not applicable; LBF = leg blood flow; HR = heart rate; VO_2 = volume of oxygen consumed; [La] = lactate concentration; W = Watts; a-v O_2 = arteriovenous oxygen difference; SL = sea level; IH = intermittent hypoxia; and Hb_{mass} = total hemoglobin mass.

Table 2. Summary of studies that have examined the effect of hemodilution on exercise capacity in

a hypoxic environment. NS = not significant (unless specified, all data presented represents a significant change); RCV = red blood cell volume; Δ = change; Htc = percent Htc; [Hb] = Hb concentration; CaO_2 = arterial oxygen content; WB = whole body; $\text{VO}_{2\text{max}}$ = maximal oxygen consumption; N/A = not applicable; kpm = kilopond per meter; V_E = minute ventilation; HR = heart rate; RER = respiratory exchange ratio; Q = cardiac output; FiO_2 = fraction of inspired oxygen; W = watts; 2LBF = two leg blood flow; SVC = systemic vascular conductance; LVC = leg vascular conductance; and MAP = mean arterial pressure.

Table 3. Summary of studies that have examined the effect of red blood cell volume (RCV) on

exercise capacity in a hypoxic environment. NS = not significant (unless specified, all data presented represents a significant change); Δ = change; Htc = percent Htc; [Hb] = Hb concentration; CaO_2 = arterial oxygen content; WB = whole body; $\text{VO}_{2\text{max}}$ = maximal oxygen consumption; Tx =

treatment; HR = heart rate; N/A = not applicable; [La] = lactate concentration; FiO_2 = fraction of inspired oxygen; and TTE = time to exhaustion.

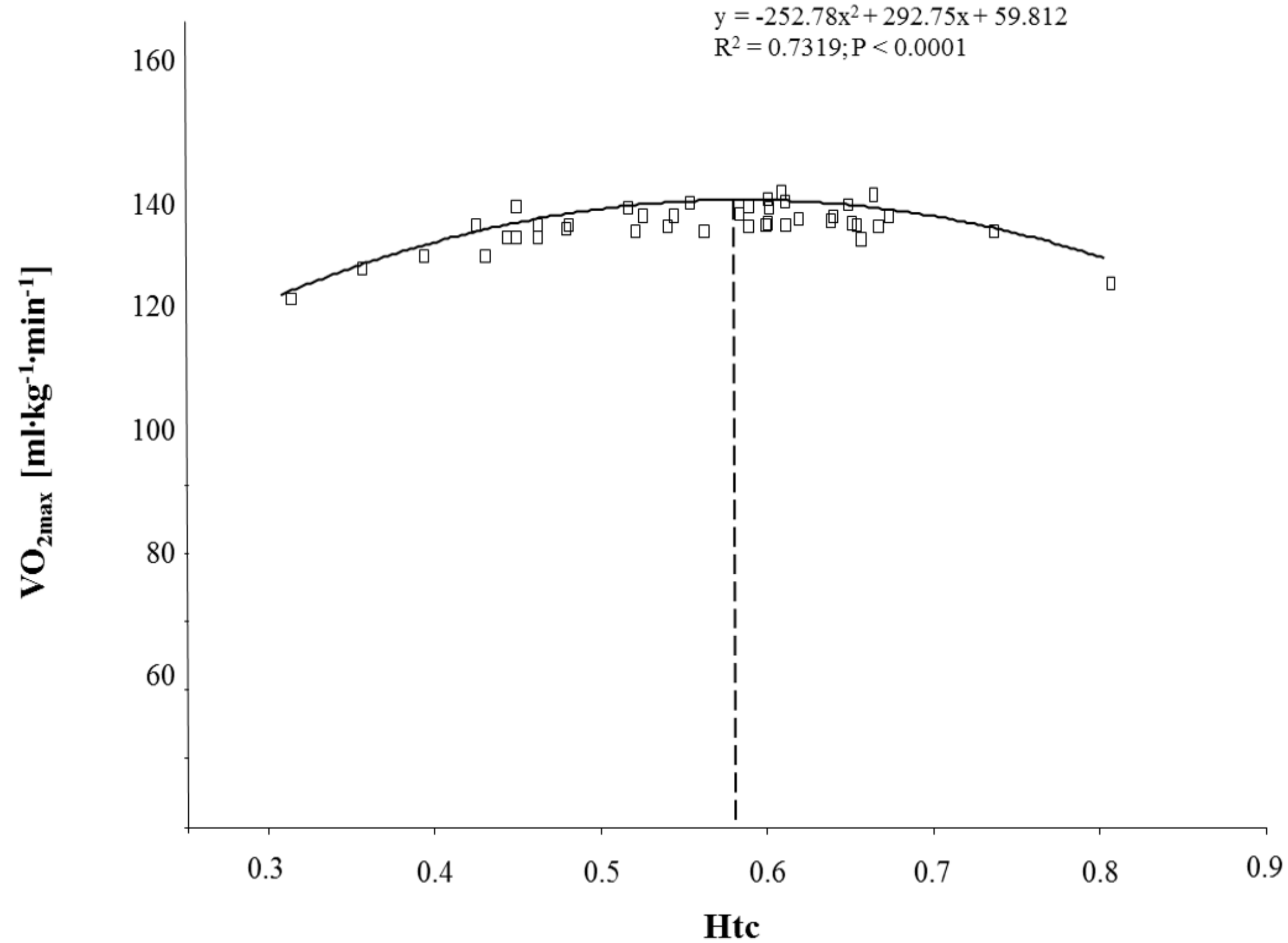
Table 4. Summary of studies that have examined the effect of erythropoietic stimulating agent (ESA) on exercise capacity in a hypoxic environment. *Values obtained during maximal exercise. NS = not significant (unless specified, all data presented represents a significant change); RCV = red blood cell volume; Δ = change; Htc = percent Htc; [Hb] = Hb concentration; CaO_2 = arterial oxygen content; WB = whole body; $\text{VO}_{2\text{max}}$ = maximal oxygen consumption; NESP = novel erythropoiesis stimulating protein; rhEpo = recombinant human erythropoietin; W = watts; RER = respiratory exchange ratio; N/A = not applicable; [La] = lactate concentration; and FiO_2 = fraction of inspired oxygen.

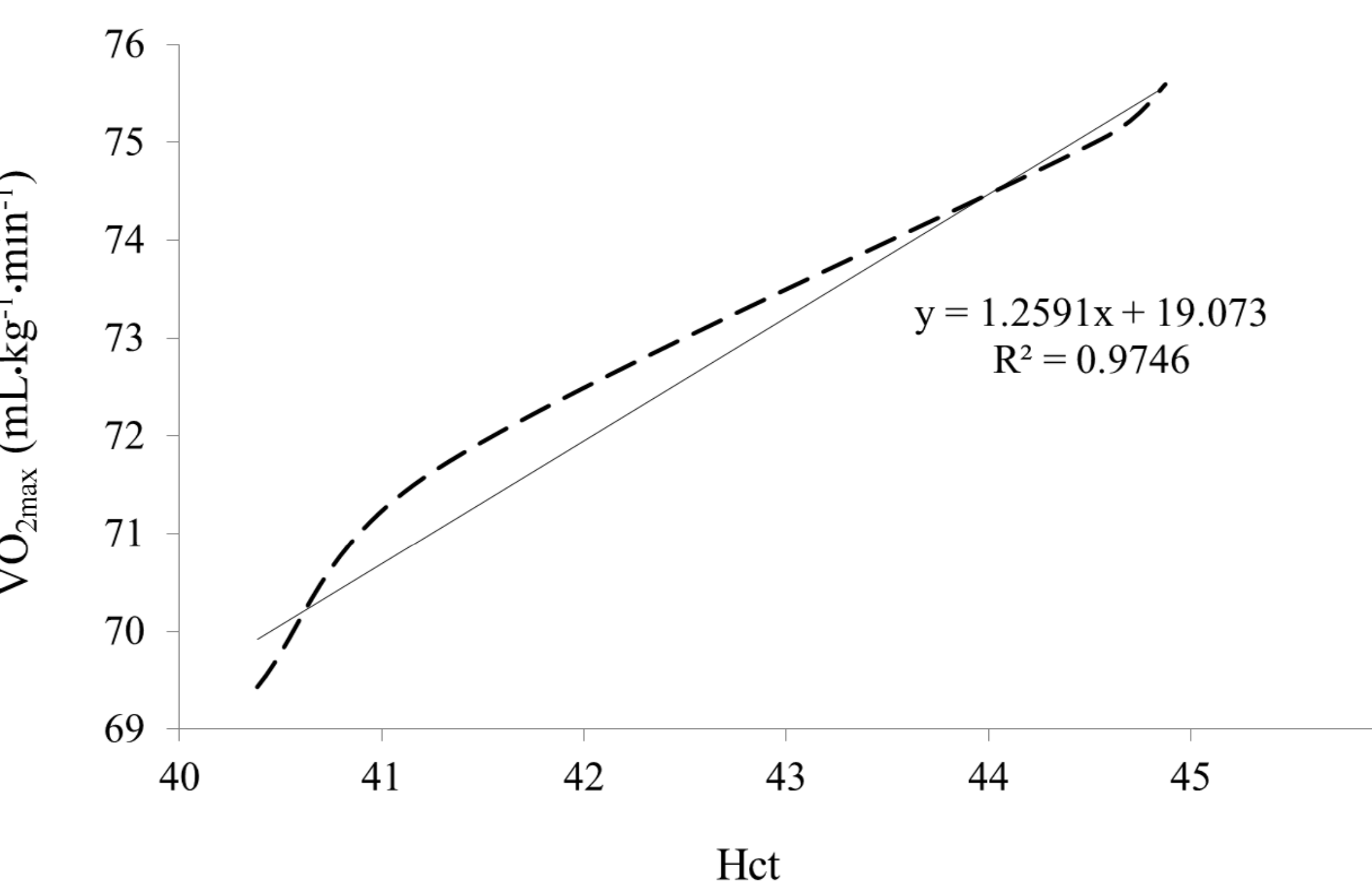
Table 5. Changes in hematopoietic characteristics and maximal oxygen consumption at various degrees of hypoxic exposure. * $P < 0.05$ pre recombinant human erythropoietin (rHuEpo) treatment versus post rHuEpo treatment. Percent hematocrit = Htc; Δ = change; CaO_2 = arterial oxygen content; and $\text{VO}_{2\text{max}}$ = maximal oxygen consumption. Data obtained from reference ¹⁶.

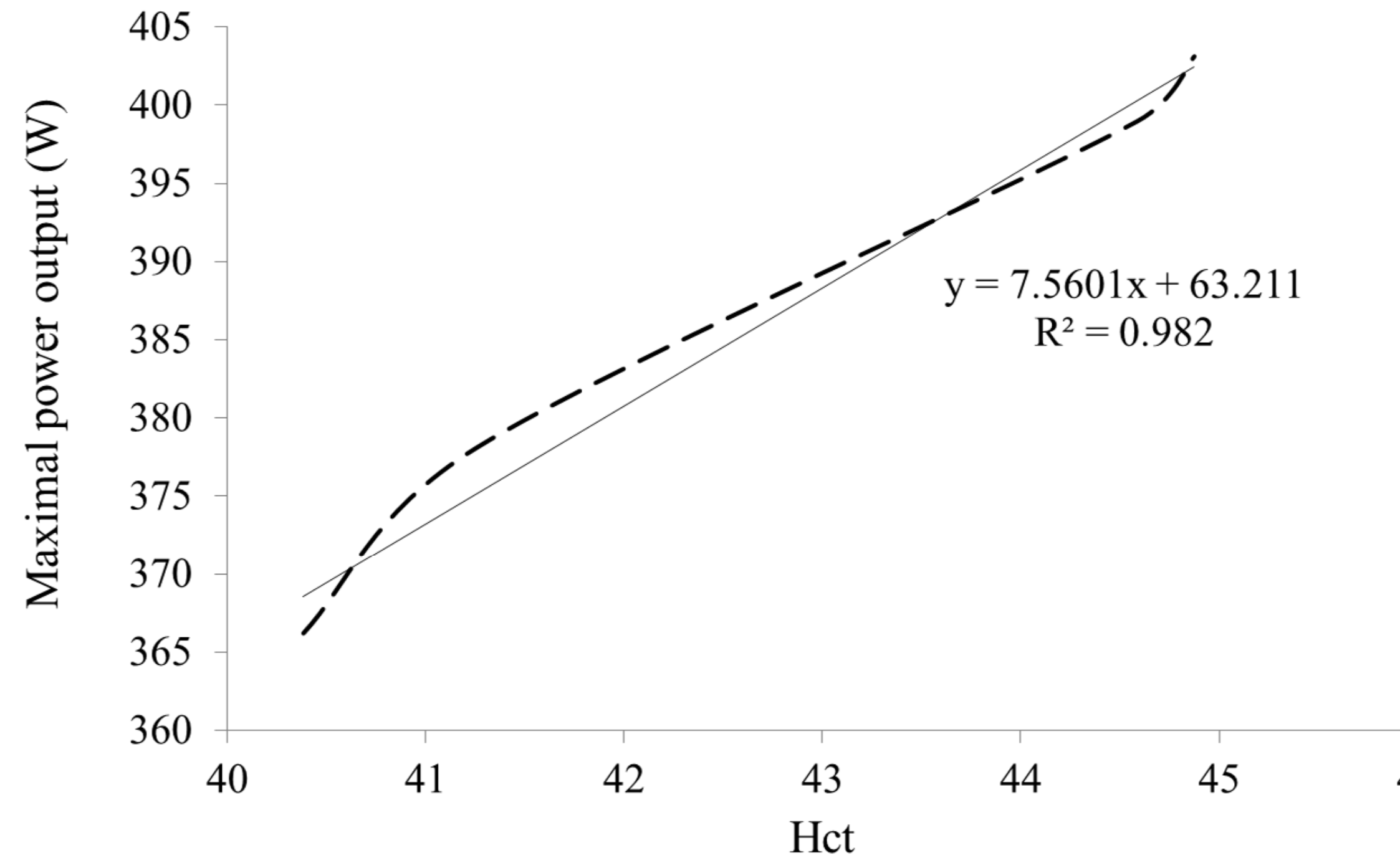
Figure Legends

Figure 1. Relationship between maximal aerobic capacity ($\text{VO}_{2\text{max}}$) and percent hematocrit (Htc) in wild type mice following either injection with erythropoietic stimulating agent (ESA) or blood withdrawal. Adapted from reference ⁴⁴.

Figure 2A-C. Correlation between percent hematocrit (Htc) and **A.** maximal oxygen consumption ($\text{VO}_{2\text{max}}$); **B.** maximal power output in Watts (W); and **C.** time to exhaustion (TTE). Data obtained from reference ⁸². Individual subject responses ($n = 7$) for maximal power output (*A*), $\text{VO}_{2\text{max}}$ (*B*) and TTE (*C*) during constant-load cycling. Subjects were tested at sea level and again on days 1, 7, 14 and 21 after arrival at 2,340 m.







TIME (min)

37
36
35
34
33
32
31

40

41

42

43

44

45

Hct

$$y = 0.8399x - 1.7483$$
$$R^2 = 0.935$$

